Elemental impurity limits in excipients.

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Editorial

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The United States Pharmacopeia (USP) has proposed changes to control the levels of elemental impurities in bio/pharmaceutical drugs that are included in two new USP General Chapters: USP <232> Elemental Impurities-Limits, and USP <233> Elemental Impurities-Procedures. These chapters are anticipated to replace USP General Chapter USP <231> Heavy Metals.

The proposed tests measure individual metals as opposed to a group of metals that were measured by the previous sulfide precipitation method USP <231>. Most manufacturers are likely to have little or no data on *individual* metal elemental impurities in their excipient batches. Consequently, there is no assurance that such data, even assuming that it could be generated across multiple manufacturers/lots/geographical locations in a short period of time, will meet the proposed limits. It should be noted that these proposed limits are themselves solely set based on toxicity (permissible daily exposure, PDE) data with no regard to whether or not they are achievable, especially in mined or natural sourced excipients. Should it turn out that one or more of the proposed individual metal specifications are not achievable, this may force the withdrawal of mined or naturally sourced excipients from the pharmaceutical markets, which by all accounts, constitutes a minor portion of the revenue stream for such commoditized and mass produced materials.

Although USP <232> recognizes the phenomenon of speciation in metals, the proposed methods can detect only the total metal content (not individual species) and assume the presence of only the inorganic form in the test material. The proposed methods therefore do not seem to be able to distinguish between the bioavailable fraction versus the total metal content in the test material. Recombinant modified bacteria expressing luminescence encoding genes have been developed for ecotoxicological analysis that can specifically detect bioavailable fractions of cadmium, mercury and lead. Preliminary studies using the most commonly mined and naturally sourced excipients would have readily established what portion of the heavy metals in these processed materials was bioavailable. This information could have been used as a basis for

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setting data driven meaningful specficiations. Measuring total metal content is not useful if a very small fraction is actually bioavailable, in which case the existing USP <231> may very well suffice to adequately control metal impurities.

The International Conference on Harmonization (ICH) is working on a new guideline on metal impurities, ICH Q3D. This guideline will ensure that specifications for metal impurities will be consistent across the United States, Europe and Japan. The approved guideline is expected to be available in 2014 at the earliest. Stakeholders have persistently expressed their opinion that the USP guidelines in USP <232> and USP <233> be harmonized, or at least take into account the ICH effort so that USP requirements align in large part with those that will eventually be applied with the finalization of ICH Q3D.

USP <232> states that testing is not needed if manufacturers can demonstrate the absence of impurities by validated processes and supply-chain control. The caveat of validated processes presumably incorporates individual metal testing. Given that there may exist significant variability in individual metals for mined or naturally sourced excipients (mined or harvested from different geographical regions or even from different locations in the same quarry or plantation), there can be no assurance that a particular batch may consistently meet specifications for any individual metal, regardless of the (scramble to) develop validated analytical procedures; that themselves require costly instrumentation. Therefore, the argument that the newly developed chapters allow for a risk based management approach is misleading. A better approach would have been to allow for outliers in an overall robust statistical risk analysis from various batches across different locations.

USP <232> states that the proposed limits are based on chronic exposure. Does this imply that chemotherapeutic, antibiotic, anesthetic or antimalarial medicines, or those that are not for prophylactic use, would be exempt from these limits? For those patients on long term life saving cardiovascular, antidiabetic or antiHIV medications, would it matter if the total metal content of sulfide precipitation enabled heavy metal impurities in the drug product was below a reasonably stringent threshold, and had been so for decades without any ill effects, or would they want metal impurities to be individually quantified? What would be the risk to benefit ratio of doing so? Even assuming that particular metals in this sulfide precipitation enabling cocktail were greater than their PDE limits, while meeting the (admittedly subjective) total metal content specification of USP <231>, there may be other methods available that would not necessarily require expensive instrumentation such as ICP-AES or ICP-OES to measure individual metals. Such methods can be developed based on fractional precipitation of individual metals due to their different solubility products and would, in all probability, be implemented using an inexpensive titrimetric method in conjunction with ion specific electrodes. A large sample size (2 grams for a limit of 10 parts per million (ppm)) for excipients is not unduly cumbersome (as it is in the case of proteins or peptide APIs). Therefore, the testing can incorporate large sample sizes *in leu* of more expensive instrumented methodology if applicable.

This brings us to the last, but not (by any means) the least important question. Is this nuanced level of regulation really necessary? The mean daily intake of arsenic in food for adults has been estimated to range from 16.7 to 129 μg ((1) and references therein). A number of estimates based on figures for per capita consumption have been made of the daily dietary lead intake, for example, 27 μg/day in Sweden, 66 μg/day in Finland, and 53.8 μg/day from food for adolescents and adults in Canada. In some countries, dietary intakes of lead as high as 500 μg/day have been reported. The regular consumption of wine can also result in a significant increase in lead intake, an

average level of 73 μg/l has been reported ((2) and references therein). The proposed individual oral PDE limits for arsenic and lead in USP <232> seems unduly low in this respect. Levels of heavy metals in (<125 μm readily redispersable and respirable fraction) the street dust of Cairo exceed the PDE limits with lead, arsenic and cadmium levels of 234.6, 1.52 and 0.82 ppm respectively. These are especially dangerous because they are present in easily absorbable smaller inhalable fractions and people are exposed to them on a daily (chronic) basis. The proposed tests apply to the United States, Europe and Japan, pharmaceutical products produced in these jurisdictions are sold across the world. While recognizing that these examples can hardly be used as justification for not controlling heavy metals in excipients, it may be prudent to ask whether regulation at this non-consequential, yet widely differential a scale, would make any significant difference to the heavy metal ingestion of the general global populace, given the exponentially rising levels of urbanization, industrialization and of motorized vehicles.

This detailed a level of regulation introduces unnecessary logistical problems. Some of these include the necessity to 'pick and choose' lots for sale or consumption based on their individual heavy metal content and the (bio)pharmaceutical products they are destined to be part of. Where the total limit for an individual metal is exceeded, additional testing is necessary to demonstrate that the bioavailable species (depending on the route of administration) meets the specifications. Designation of additional in-house identification numbers, inventory control and management for excipient lots is necessary depending on their destination of use, i.e., in oral, parenteral or inhalation formulation batches. All these have to fall in place in conjunction with API stability considerations, additional impurity specification regulations and whether or not monographs are harmonized across the various jurisdictions, necessitating additional documentation, verification, validation (and if necessary, requalification) ,bureaucracy and an increase in the cost of medicines.

By all accounts, analytical limit testing in USP <231> has rarely produced positive results, implying that no individual metal was present at a higher specified limit. Although there were issues with the accuracy and recovery of metals, particularly mercury, using the sulfide precipitation method, does a risk that is neither clearly identified nor significant to the health of patients as demonstrated over time, necessitate imposition of new analytical methodology that has concomitant specifications that impact supply chains and has repercussions far beyond its ostensible modest purview? Regardless of whether or not USP <232> and USP <233> will eventually harmonize with ICH Q3D, new regulation and mandates must have clearly defined and measurable value that is significantly better than that existing, that is acknowledged by all stakeholders, a reasonable risk to reward outcome, and ease of adoption and implementation.

REEFERENCES

1. World Health Organization, Arsenic in Drinking Water, WHO/SDE/WSH/03.04/75/Rev/1, 2011

2. World Health Organization, Lead in Drinking-water, WHO/SDE/WSH/03.04/09/Rev/1, 2011